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| NEWS 3 | Feb 06 | Engineering Information Encompass files have new names |
| NEWS 4 | Feb 16 | TOXLINE no longer being updated |
| NEWS 5 | Apr 23 | Search Derwent WPINDEX by chemical structure |
| NEWS 6 | Apr 23 | PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA |
| NEWS 7 | May 07 | DGENE Reload |
| NEWS 8 | Jun 20 | Published patent applications (A1) are now in USPATFULL |
| NEWS 9 | JUL 13 | New SDI alert frequency now available in Derwent's DWPI and DPCI |
| NEWS 10 | Aug 23 | In-process records and more frequent updates now in MEDLINE |
| NEWS 11 | Aug 23 | PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA |
| NEWS 12 | Aug 23 | Adis Newsletters (ADISNEWS) now available on STN |

| | |
|---|---|
| NEWS EXPRESS | August 15 CURRENT WINDOWS VERSION IS V6.0c, CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP), AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001 |
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| NEWS LOGIN | Welcome Banner and News Items |
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FILE 'HOME' ENTERED AT 10:38:12 ON 06 SEP 2001

=> file medline, uspat,hcaplus, wpids, dgene, embase, frosti, fsta,

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|---|---|---|
| FULL ESTIMATED COST | 0.30 | 0.30 |

FILE 'MEDLINE' ENTERED AT 10:39:15 ON 06 SEP 2001

FILE 'USPATFULL' ENTERED AT 10:39:15 ON 06 SEP 2001
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=> s coronary artery disease

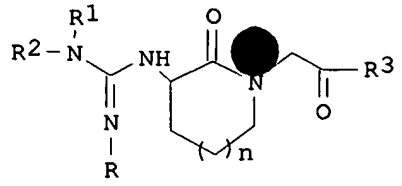
L1 75286 CORONARY ARTERY DISEASE

=> s coronary artery disease () treatment () method

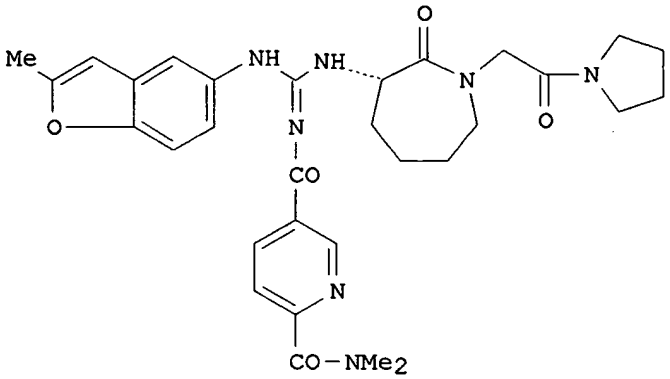
4 FILES SEARCHED...
L2 1 CORONARY ARTERY DISEASE (W) TREATMENT (W) METHOD

=> d l2 ti abs ibib tot

L2 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2001 ACS
TI Preparation of caprolactams, piperidinones, and pyrrolidinones as Factor Xa inhibitors in prevention or treatment of thromboses, coronary artery disease, or cerebrovascular disease in mammals
GI



I



II

AB Title chiral compds. [I; R = CN, CONH2, COOCH2CH3, COC6H5, SO2NH2, OCH3, SO2N(CH3)2, SO2CH3, arylsulfonyl, heterocyclosulfonyl, (un)substituted Ph, heterocyclyl, heterocycleocarbonyl, alkoxylcarbonyl, arylaminocarbonyl; R1 = H, arylalkyl; R2 = alkyl, (un)substituted Ph, benzoheterocyclyl, cyclopentyl; R3 = heterocyclylamino, heterocyclyl, alkoxy, cycloalkylamino, OH; n = 0, 1, 2] , pharmaceutically acceptable salts, and stereoisomers are pred. as Factor Xa inhibitors and are useful as anticoagulants (no data). A method for treating cardiovascular diseases assocd. with thromboses is also provided. Thus, the title compd. II was prepd.

ACCESSION NUMBER: 2000:573666 HCAPLUS
DOCUMENT NUMBER: 133:164010
TITLE: Preparation of caprolactams, piperidinones, and pyrrolidinones as Factor Xa inhibitors in prevention or treatment of thromboses, coronary artery disease, or cerebrovascular disease in mammals
INVENTOR(S): Stein, Philip D.; Bisacchi, Gregory S.; Shi, Yan; O'Connor, Stephen P.; Li, Chi
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 284 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000047207 | A1 | 20000817 | WO 2000-US2883 | 20000202 |

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-119372 P 19990209
US 1999-167428 P 19991124
OTHER SOURCE(S): MARPAT 133:164010
REFERENCE COUNT: 2
REFERENCE(S): (1) Lowe; US 5484917 A 1996 HCAPLUS
(2) Lowe; US 5618811 A 1997 HCAPLUS

=> d his

(FILE 'HOME' ENTERED AT 10:38:12 ON 06 SEP 2001)

FILE 'MEDLINE, USPATFULL, HCAPLUS, WPIDS, DGENE, EMBASE, FROSTI, FSTA'
ENTERED AT 10:39:15 ON 06 SEP 2001
L1 75286 S CORONARY ARTERY DISEASE
L2 1 S CORONARY ARTERY DISEASE () TREATMENT () METHOD

=> s l1 and FGF-2

4 FILES SEARCHED...
L3 19 L1 AND FGF-2

=> d l3 ti abs ibib tot

L3 ANSWER 1 OF 19 USPATFULL
TI Platelet derived growth factor (PDGF) nucleic acid ligand complexes
AB This invention discloses a method for preparing a complex comprised of a
PDGF Nucleic Acid Ligand and a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound by identifying a PDGF Nucleic Acid Ligand by SELEX methodology and associating the PDGF Nucleic Acid Ligand
with a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound. The invention further discloses Complexes comprising one or more PDGF Nucleic Acid Ligands in association with a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound. The invention further includes a Lipid construct comprising a PDGF Nucleic Acid Ligand
or Complex and methods for making the same.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:67813 USPATFULL
TITLE: Platelet derived growth factor (PDGF) nucleic acid ligand complexes
INVENTOR(S): Janjic, Nebojsa, Boulder, CO, United States
Gold, Larry, Boulder, CO, United States
PATENT ASSIGNEE(S): NeXstar Pharmaceuticlas, Inc., Boulder, CO, United States (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 6229002 | B1 | 20010508 |
| APPLICATION INFO.: | US 1997-991743 | | 19971216 (8) |

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1996-618693, filed on 20 Mar 1996, now patented, Pat. No. US 5723594
Continuation-in-part of Ser. No. US 1995-479783, filed on 7 Jun 1995, now patented, Pat. No. US 5668264
Continuation-in-part of Ser. No. US 1995-479725, filed on 7 Jun 1995, now patented, Pat. No. US 5674685
DOCUMENT TYPE: Utility

FILE SEGMENT: Granted
PRIMARY EXAMINER: Zitomer, Stephanie
LEGAL REPRESENTATIVE: [redacted]anson & Bratschun LLC
NUMBER OF CLAIMS: 11
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 30 Drawing Figure(s); 26 Drawing Page(s)
LINE COUNT: 3002
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2001 ACS
TI Pharmacokinetics and pharmacodynamics of recombinant **FGF-2** in a Phase I trial in **coronary artery disease**
AB Fibroblast growth factor-2 (**FGF-2**) is a heparin-binding protein capable of inducing angiogenesis in multiple animal models of chronic ischemia. The pharmacokinetics and pharmacodynamics of a single dose of recombinant **FGF-2** (rFGF-2) administered by intracoronary or i.v. infusion were evaluated in a Phase I trial in 66 patients with severe **coronary artery disease**. RFGF-2 displayed biphasic elimination with a mean studywide distribution t1/2 of 21 min and a mean apparent terminal elimination t1/2 of 7.6 h. Systemic exposure to rFGF-2 was comparable following intracoronary or i.v. administration. Peak plasma concn. and area under the concn.-time curve increased proportionally with dose, indicating linear pharmacokinetics over the dose range examd. (0.33 to 48.0 .mu.g/kg). Greater systemic exposure was obsd. when heparin was administered closer to rFGF-2 infusion, consistent with slower clearance of heparin/rFGF-2 complexes. Infusion of rFGF-2 was assocd. with changes in acute hemodynamics. While a clear PK/PD dose-response relationship was not established, a trend toward hypotension and tachycardia with higher rFGF-2 doses was obsd.
ACCESSION NUMBER: 2001:285750 HCAPLUS
TITLE: Pharmacokinetics and pharmacodynamics of recombinant **FGF-2** in a Phase I trial in **coronary artery disease**
AUTHOR(S): Bush, Mark A.; Samara, Emil; Whitehouse, M. J.; Yoshizawa, Carl; Novicki, Deborah L.; Pike, Marilyn; Laham, Roger J.; Simons, Michael; Chronos, Nicolas A.
CORPORATE SOURCE: Chiron Corporation, Emeryville, CA, 94608-2916, USA
SOURCE: J. Clin. Pharmacol. (2001), 41(4), 378-385
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 22
REFERENCE(S):
(1) Burgess, W; Annu Rev Biochem 1989, V58, P575 HCAPLUS
(2) Cuevas, P; Science 1991, V254, P1208 HCAPLUS
(3) Faham, S; Science 1996, V271, P1116 HCAPLUS
(6) Laham, R; Circulation 1999, V100(18), P1865 HCAPLUS
(7) Laham, R; Drug Metab Dispos 1999, V27(7), P821 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2001 ACS
TI Angiogenically effective unit dose of fibroblast growth factor-2 and method of use
AB The present invention has multiple aspects. In particular, in one aspect, the present invention is directed to a unit dose compn. comprising 0.2 <mg/kg to 48 <mg/kg of bovine **FGF-2** or an angiogenically active fragment or mutein thereof in a pharmaceutically

acceptable carrier. In another aspect, the present invention is directed to a method for treating a human patient for **coronary artery disease**, comprising administering into one or more coronary vessels or a peripheral vein of a human patient in need of treatment for **coronary artery disease** a safe and angiogenically ED of a recombinant **FGF-2**, or an angiogenically active fragment or mutein thereof. The single unit dose compn. of the present invention provides an angiogenic effect in a human CAD patient that lasts six months before re-treatment is required. In another aspect, the present invention is directed to a method of administration which optimizes patient's safety. In this embodiment, fluids, heparin and/or rate of infusion all play a role. In another aspect, the present invention is directed to a pharmaceutical compn. comprising a therapeutically effective amt. of **FGF-2**, alone or in combination with heparin, in a therapeutically effective carrier. The magnitude and duration of benefit were unexpected; in addn. benefit with the IV route was unexpected.

ACCESSION NUMBER: 2000:175692 HCAPLUS
DOCUMENT NUMBER: 132:227446
TITLE: Angiogenically effective unit dose of fibroblast growth factor-2 and method of use
INVENTOR(S): Whitehouse, Martha Jo
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000013701 | A2 | 20000316 | WO 1999-US19770 | 19990827 |
| WO 2000013701 | A3 | 20000803 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9960223 | A1 | 20000327 | AU 1999-60223 | 19990827 |
| EP 1121142 | A2 | 20010808 | EP 1999-968630 | 19990827 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1998-145743 | P | 19980903 |
| US 1998-104102 | P | 19981013 |
| US 1998-104103 | P | 19981013 |
| WO 1999-US19770 | W | 19990827 |

L3 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2001 ACS
TI Angiogenesis in cardiovascular disease: current status and therapeutic potential
AB A review with 34 refs. Therapeutic angiogenesis, in the form of growth factor protein administration or gene therapy, has emerged as a new method of treatment for patients with severe, inoperable **coronary artery disease**. Improved myocardial perfusion and function after the administration of angiogenic growth factors has been demonstrated in animal models of chronic myocardial ischemia. Recently, preliminary clin. trials using growth factor proteins or genes encoding these angiogenic factors have demonstrated clin. and other objective

evidence of relevant angiogenesis. Thus, therapeutic angiogenesis has the potential to extend treatment options to patients who are not optimal candidates for conventional methods of myocardial revascularization.

ACCESSION NUMBER: 1999:641878 HCAPLUS
DOCUMENT NUMBER: 131:252631
TITLE: Angiogenesis in cardiovascular disease: current status and therapeutic potential
AUTHOR(S): Sellke, Frank W.; Simons, Michael
CORPORATE SOURCE: Beth Israel Deaconess Medical Center, Division of Cardiothoracic Surgery and Cardiovascular Division, Harvard Medical School, Boston, MA, USA
SOURCE: Drugs (1999), 58(3), 391-396
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 34
REFERENCE(S): (2) Banai, S; Circulation 1994, V89(5), P2183 HCAPLUS
(5) Harada, K; Am J Physiol 1996, V270, PH1791 HCAPLUS
(6) Harada, K; J Clin Invest 1994, V94, P623 HCAPLUS
(9) Ishikawa, F; Nature 1989, V338, P557 HCAPLUS
(11) Klagsbrun, M; Annu Rev Physiol 1991, V53, P217 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2001 ACS
TI Elastase and elastase inhibitors and pulmonary and **coronary artery disease**
AB A review with 20 refs. Background. Increased elastolytic activity is assocd. with development and progression of pulmonary hypertension in exptl. animals. Elastase inhibitors prevent the development of pulmonary vascular disease in exptl. models. Endogenous vascular elastase appears to be an enzyme 20 kDa in mol. wt., is expressed by smooth muscle cells (SMC) and is a serine proteinase related structurally to the adipocyte enzyme, adipsin. Methods. We used cell-culture systems to det. the mechanisms whereby elastase is released and induces vascular disease in pulmonary as well as coronary arteries. Results. Elastase is induced by serum factors including apolipoprotein A1 (apo A1). The signaling mechanisms involve induction of the MAP-kinase pathway with increased expression of the transcription factor AML1. Increased activity of elastase results in the release of mitogens from the extracellular matrix such as basic fibroblast growth factor (**FGF-2**). Elastases in concert with matrix metalloproteinases can proteolyze collagen leading to the upregulation of the glycoprotein, tenascin, which is necessary to amplify the proliferative response to growth factors. The mechanism involves .beta.3-integrin-mediated signaling of the matrix glycoprotein tenascin. Elastin peptides upregulate fibronectin prodn., which is necessary for smooth muscle cell migration. Elastin peptides synergize with the cytokine interleukin 1.beta. in inducing fibronectin in coronary artery SMC. Conclusions. Since our other studies have shown that elastase inhibitors prevent the development of **coronary artery disease** exptl. induced after cardiac transplant, these enzymes might be implicated in other conditions with rapid development of neointimal formation such as restenosis.

ACCESSION NUMBER: 1998:539034 HCAPLUS
DOCUMENT NUMBER: 129:288788
TITLE: Elastase and elastase inhibitors and pulmonary and **coronary artery disease**
AUTHOR(S): Rabinovitch, Marlene

CORPORATE SOURCE: Division of Cardiovascular Research, University of Toronto, Toronto, Can.
SOURCE: Int. Congr. Ser. (1998), 1155(Atherosclerosis XI), 317-326
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

L3 ANSWER 6 OF 19 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
TI New pharmaceutical composition comprising an angiogenic agent in a range of 5-135,000 ng, useful for e.g. increasing vascular perfusion or vascular density in the myocardium, or for treating **coronary artery disease**.
AN 2001-218366 [22] WPIDS
AB WO 200113031 A UPAB: 20010421
NOVELTY - A pharmaceutical composition comprising 5-135,000 ng angiogenic agent and a carrier, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) methods for increasing vascular perfusion or density in the myocardium, or for inducing angiogenesis in a heart of a patient comprising injecting an angiogenic agent to the myocardium;
(2) a method for stimulating the production of **FGF-2** and VEGF in human myocardial cells for up to 3 months, comprising injecting an angiogenic agent directly into the myocardium of the patient in one or more areas in need of angiogenesis; and
(3) a method for treating a human patient for **coronary artery disease** by injecting an angiogenic agent in one or more areas in need of treatment for the disease. The amount of angiogenic agent is 5-135,000 ng.
ACTIVITY - Cardiant; cardiovascular.
Recombinant **FGF-2** was administered to 52 human patients with severe **coronary artery disease**, who remained symptomatic despite optimal medical management and who refused or were suboptimal candidates for surgical or percutaneous revascularization. Drug was administered as a single 20 min infusion divided between 2 major sources of coronary blood supply (IC). End points such as magnetic resonance imaging (MRI), normal wall motion (NWM), targeted wall motion (TWM), normal wall thickness (NWT), and targeted wall thickness (TWT). MRI showed objective improvements following administration of a single unit dose of the **FGF-2**, including increased TWM at 30 and 60 days, and TWM at 60 days. MRI further showed improved regional wall motion, and increased myocardial perfusion and collateral development in the targeted area for both the lower dose (0.33 micro g/kg and 0.65 micro g/kg) and higher dose (2.0 micro g/kg and 12.0 micro g/kg) groups in an 11 patient test group.
MECHANISM OF ACTION - None given.
USE - The angiogenic agent is useful for inducing angiogenesis in a human patient with symptoms of **coronary artery disease** or myocardial infarction. The angiogenic agent is also useful for increasing vascular perfusion or density in the myocardium, for stimulating the production of **FGF-2** and VEGF in human myocardial cells and for treating a human patient for **coronary artery disease**.
Dwg.0/11
ACCESSION NUMBER: 2001-218366 [22] WPIDS
DOC. NO. NON-CPI: N2001-155654
DOC. NO. CPI: C2001-065200
TITLE: New pharmaceutical composition comprising an angiogenic

agent in a range of 5-135,000 ng, useful for e.g. increasing vascular perfusion or vascular density in the myocardium, or for treating **coronary artery disease.**

DERWENT CLASS: B04 Q69
INVENTOR(S): ANNEX, B H; HUNG, D T; KAVANAUGH, W M; LANDOLFO, K P
PATENT ASSIGNEE(S): (CHIR) CHIRON CORP
COUNTRY COUNT: 93
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2001013031 | A2 | 20010222 | (200122)* | EN | 102 |

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2000066344 A 20010313 (200134)

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2001013031 | A2 | WO 2000-US22039 | 20000811 |
| AU 2000066344 | A | AU 2000-66344 | 20000811 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 2000066344 | A | Based on | WO 200113031 |

PRIORITY APPLN. INFO: US 1999-148746 19990813

L3 ANSWER 7 OF 19 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
TI Enhancing collateral growth of collateral arteries and arteries from pre-existing arteriolar connections, using monocytes loaded with arteriogenic polypeptides, useful e.g. for treating cerebral occlusive and peripheral occlusive disease.
AN 2000-619171 [59] WPIDS
CR 2000-619148 [58]
AB WO 200060054 A UPAB: 20001117
NOVELTY - A composition (I) comprising a circulating blood cell (preferably a monocyte) loaded with a therapeutically active molecule (and optionally a carrier or diluent), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) the use of a circulating blood cell (preferably a monocyte) loaded with a therapeutically active molecule for the preparation of a composition (i.e. (I)) for enhancing collateral growth of collateral arteries and/or arteries from pre-existing arteriolar connections or for treating an occlusive disease (i.e. arterial occlusive disease, e.g. **coronary artery disease**, cerebral occlusive disease, peripheral occlusive disease, visceral occlusive disease, renal artery disease or mesenterial arterial insufficiency);

(2) a kit comprising (I) and in a different compartment another composition comprising a circulating blood cell, preferably a monocyte chemotactic protein (sic);

(3) a diagnostic composition comprising a circulating blood cell, preferably a monocyte loaded with a detectable molecule;

(4) the use of a circulating blood cell, preferably a monocyte loaded

with a detectable molecule for the preparation of a diagnostic composition
for detecting collateral growth of collateral arteries and/or arteries from pre-existing arteriolar connections;
(5) use of a circulating blood cell, preferably a monocyte loaded with a detectable molecule for the preparation of a diagnostic composition
for detecting a vessel occlusion; and
(6) a method for detecting collateral growth of collateral arteries and/or arteries from pre-existing arteriolar connections, and/or detecting
and/or diagnosing a vessel occlusion, comprising the detection of microspheres originally contained in the circulating blood cells in the arteries and/or occlusions.
ACTIVITY - Angiogenic; vasotropic; cardiant.
MECHANISM OF ACTION - Stimulation of angiogenesis.
No relevant biological data given.
USE - (I) is used for enhancing collateral growth of collateral arteries and/or arteries from pre-existing arteriolar connections or for treating an occlusive disease (i.e. arterial occlusive disease, e.g. **coronary artery disease**, cerebral occlusive disease, peripheral occlusive disease, visceral occlusive disease, renal artery disease or mesenterial arterial insufficiency) (claimed).
Dwg.0/2

ACCESSION NUMBER: 2000-619171 [59] WPIDS
CROSS REFERENCE: 2000-619148 [58]
DOC. NO. CPI: C2000-185530
TITLE: Enhancing collateral growth of collateral arteries and arteries from pre-existing arteriolar connections, using monocytes loaded with arteriogenic polypeptides, useful e.g. for treating cerebral occlusive and peripheral occlusive disease.
DERWENT CLASS: B04 D16 J04
INVENTOR(S): BUSCHMANN, I; SCHAPER, W
PATENT ASSIGNEE(S): (PLAC) MAX PLANCK GES FOERDERUNG WISSENSCHAFTEN
COUNTRY COUNT: 89
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2000060054 | A1 | 20001012 | (200059)* | EN | 30 |
| RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE | | | | | |
| W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW | | | | | |
| AU 2000045446 | A | 20001023 | (200107) | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2000060054 | A1 | WO 2000-EP3087 | 20000406 |
| AU 2000045446 | A | AU 2000-45446 | 20000406 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---|---|---|
| AU 2000045446 | A Based on | WO 200060054 |

PRIORITY APPLN. INFO: EP 1999-106800 19990406

L3 ANSWER 8 OF 19 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

TI Novel unit dose comprising fibroblast growth factor, its angiogenically active fragment or mutein for inducing cardiac angiogenesis, treating **coronary artery disease** and reducing post myocardial infarction injury.

AN 2000-317840 [27] WPIDS

CR 2000-256860 [22]

AB WO 200021548 A UPAB: 20010815

NOVELTY - Unit dose (I), of fibroblast growth factor (FGF) comprising 0.008-6.1 mg of a mammalian FGF comprising sequence of 140 ((II) and (III)), 146 ((IV) and (V)), 205 (VI), 266 (VII), 207 ((VIII) and (XI)), 215 (IX), and 208 (X) amino acids (aa), given in the specification, its angiogenically active fragment or mutein, is new.

ACTIVITY - Angiogenic; cardiant.

The biological activity of (I) comprising FGF was tested in human patient diagnosed with **coronary artery disease** (CAD). The patients were administered a unit dose of 0.33-49 mu g/kg of bovine **FGF-2** (V) by coronary vessel (IC) infusion over a 20 minute period. The 52 treated patients were then assessed by the Seattle Angina Questionnaire. Twenty-eight patients, exhibited a mean score increase of 13-36 points for the five 'quality of life' criteria assessed by the questionnaire. These 13-36 point mean increases were 1.6-4.5 times greater than the 8 point change.

MECHANISM OF ACTION - Cardiac angiogenesis inducer.

USE - (I) is used for treating a human patient for **coronary artery disease**, and inducing angiogenesis in the human heart (claimed). (I) further provides an adjunct for reducing post myocardial infarction injury in humans.

ADVANTAGE - The unit dose provides the human patient with a rapid and therapeutic cardiac angiogenesis sufficient to obviate surgical intervention and results in an superior increase in the treated patients's exercise tolerance time (ETT). It also provides a safe and therapeutically efficacious treatment for the patients with **coronary artery disease** that lasts at least 6 months before a further treatment is needed. The method provides superior increase of 1.5-2 minutes in the treated patient's (ETT), compared to an increase of 30 seconds for current modes treatment.

Dwg.0/3

ACCESSION NUMBER: 2000-317840 [27] WPIDS

CROSS REFERENCE: 2000-256860 [22]

DOC. NO. CPI: C2000-096206

TITLE: Novel unit dose comprising fibroblast growth factor, its angiogenically active fragment or mutein for inducing cardiac angiogenesis, treating **coronary artery disease** and reducing post myocardial infarction injury.

DERWENT CLASS: B04

INVENTOR(S): KAVANAUGH, W M

PATENT ASSIGNEE(S): (CHIR) CHIRON CORP; (WHIT-I) WHITEHOUSE M J

COUNTRY COUNT: 87

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2000021548 | A2 | 20000420 | (200027)* | EN | 66 |
| RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW | | | | | |
| W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW | | | | | |
| AU 9964111 | A | 20000501 | (200036) | | |

EP 1121141 A2 20010808 (200146) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2000021548 | A2 | WO 1999-US22936 | 19991013 |
| AU 9964111 | A | AU 1999-64111 | 19991013 |
| EP 1121141 | A2 | EP 1999-951728 | 19991013 |
| | | WO 1999-US22936 | 19991013 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9964111 | A | Based on | WO 200021548 |
| EP 1121141 | A2 | Based on | WO 200021548 |

PRIORITY APPLN. INFO: US 1998-104103 19981013

L3 ANSWER 9 OF 19 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
TI Composition for inducing angiogenesis or treating **coronary artery disease** comprises fibroblast growth factor-2 or angiogenically active fragment or mutein.
AN 2000-256860 [22] WPIDS
CR 2000-317840 [27]
AB WO 200013701 A UPAB: 20010815
NOVELTY - A unit dose composition (I) for inducing angiogenesis in a human, comprising 0.008-7.2 mg of fibroblast growth factor (**FGF**)-**2** or an angiogenically active fragment or mutein, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method for treating **coronary artery disease** or inducing angiogenesis in a human patient comprising administering recombinant **FGF-2** or an angiogenically active fragment or mutein to one or more coronary vessels or to a peripheral vein in a human patient.

ACTIVITY - Cardiant; angiogenic; vasodilator; antianginal; hypotensive.

A phase 1 clinical trial directed to treating human patients for **coronary artery disease** (CAD) by administering a single unit dose composition was conducted. In that trial, 66 human patients diagnosed with CAD received a single unit dose of recombinant **FGF-2** (rFGF-2). Specifically, 52 human patients were administered a unit dose of 0.33-48 micro g/kg of rFGF-2 by intracoronary (IC) vessel infusion over a 20 minute period. Fourteen human patients were administered a unit dose of either 18 or 36 micro g/kg of rFGF-2 by intravenous (IV) infusion over a 20 minute period. The 66 treated patients were then assessed relative to baseline (prior to treatment with the single unit dose), and again at 1 month, 2 months and 6 months after treatment with the single unit dose, using three sets of assessment criteria:

(1) changes in their exercise tolerance time (ETT);
(2) the Seattle Angina Questionnaire (SAQ); and
(3) the measurement of physical changes in the heart by magnetic resonance imaging (MRI).

The human patients in this study exhibited a mean increase in ETT of 1.5 to 2 minutes. This is especially significant because an increase in ETT of greater than 30 seconds is considered significant and a benchmark for evaluating alternative therapies, such as angioplasty. The angina frequency and quality of life, as measured by SAQ, showed a significant

improvement at 2 months in all five subscales for the 66 patients (n=66) tested.

When 33 human [redacted]D patients were assessed by re[redacted]ng cardiac magnetic resonance imaging (MRI) at baseline, and at 1, 2, and 6 months after receiving a single unit dose composition of the present invention by IC or IV routes, a highly statistically significant increase was observed in target wall thickening, target wall motion and target area collateral extent; a highly statistically significant decrease was observed in target area delayed arrival extent; and no statistically significant changes were observed in normal wall motion, normal wall thickening or myocardial infarct extent.

MECHANISM OF ACTION - Administration of fibroblast growth factor (**FGF**)-**2** (or recombinant **FGF**-2) or an angiogenically active fragment or mutein is associated with the release of nitric oxide, a smooth muscle dilator, which causes a sudden drop in the patient's blood pressure.

USE - The composition (I) and recombinant **FGF-2** are useful for treating **coronary artery disease** or inducing angiogenesis in a human patient. Recombinant **FGF-2** may be used to treat unstable angina and acute myocardial infarction.

Dwg.0/5

ACCESSION NUMBER: 2000-256860 [22] WPIDS
CROSS REFERENCE: 2000-317840 [27]
DOC. NO. CPI: C2000-078434
TITLE: Composition for inducing angiogenesis or treating **coronary artery disease** comprises fibroblast growth factor-2 or angiogenically active fragment or mutein.
DERWENT CLASS: B04 D16
INVENTOR(S): WHITEHOUSE, M J
PATENT ASSIGNEE(S): (CHIR) CHIRON CORP; (WHIT-I) WHITEHOUSE M J
COUNTRY COUNT: 86
PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG |
|---|---|---|---|---|---|
| WO 2000013701 | A2 | 20000316 | (200022)* | EN | 60 |

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW

| | | | | | |
|---|---|---|---|---|---|
| AU 9960223 | A | 20000327 | (200032) | | |
| EP 1121142 | A2 | 20010808 | (200146) | EN | |

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---|---|---|---|
| WO 2000013701 | A2 | WO 1999-US19770 | 19990827 |
| AU 9960223 | A | AU 1999-60223 | 19990827 |
| EP 1121142 | A2 | EP 1999-968630 | 19990827 |
| | | WO 1999-US19770 | 19990827 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO |
|---|---|---|---|
| AU 9960223 | A | Based on | WO 200013701 |
| EP 1121142 | A2 | Based on | WO 200013701 |

PRIORITY APPLN. INFO: US 1998-104103 19981013; US 1998-145743 19980903; US 1998-104102 19981013

L3 ANSWER 10 OF 19 DGENE COPYRIGHT 2001 DERWENT INFORMATION LTD
TI Composition for inducing angiogenesis or treating **coronary artery disease** comprises fibroblast growth factor-2 or angiogenically active fragment or mutein -
AB This sequence represents a fragment of a recombinant bovine fibroblast growth factor-2 (**FGF-2**). The invention relates to a unit dose composition (I) for inducing angiogenesis in a human, comprising 0.008-7.2 mg of **FGF-2** or an angiogenically active fragment or mutein of **FGF-2**. The composition (I) and recombinant **FGF-2** are useful for treating **coronary artery disease** or inducing angiogenesis in a human patient. Recombinant **FGF-2** may be used to treat unstable angina and acute myocardial infarction.
ACCESSION NUMBER: AAY81942 Peptide DGENE
TITLE: Composition for inducing angiogenesis or treating **coronary artery disease** comprises fibroblast growth factor-2 or angiogenically active fragment or mutein -
PATENT ASSIGNEE: (CHIR)CHIRON CORP.
(WHIT-I) WHITEHOUSE M J.
PATENT INFO: WO 2000013701 A2 20000316 60p
APPLICATION INFO: WO 1999-US19770 19990827
PRIORITY INFO: US 1998-145743 19980903
US 1998-104102 19981013
US 1998-104103 19981013
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-256860 [22]

L3 ANSWER 11 OF 19 DGENE COPYRIGHT 2001 DERWENT INFORMATION LTD
TI Composition for inducing angiogenesis or treating **coronary artery disease** comprises fibroblast growth factor-2 or angiogenically active fragment or mutein -
AB This sequence represents a recombinant bovine fibroblast growth factor-2 (**FGF-2**) sequence. The invention relates to a unit dose composition (I) for inducing angiogenesis in a human, comprising 0.008-7.2 mg of **FGF-2** or an angiogenically active fragment or mutein of **FGF-2**. The composition (I) and recombinant **FGF-2** are useful for treating **coronary artery disease** or inducing angiogenesis in a human patient. Recombinant **FGF-2** may be used to treat unstable angina and acute myocardial infarction.
ACCESSION NUMBER: AAY81941 Protein DGENE
TITLE: Composition for inducing angiogenesis or treating **coronary artery disease** comprises fibroblast growth factor-2 or angiogenically active fragment or mutein -
PATENT ASSIGNEE: (CHIR)CHIRON CORP.
(WHIT-I) WHITEHOUSE M J.
PATENT INFO: WO 2000013701 A2 20000316 60p
APPLICATION INFO: WO 1999-US19770 19990827
PRIORITY INFO: US 1998-145743 19980903
US 1998-104102 19981013
US 1998-104103 19981013
DOCUMENT TYPE: Patent
LANGUAGE: English

OTHER SOURCE: 2000-256860 [22]

L3 ANSWER 12 OF 19 DGENE COPYRIGHT 2001 DERWENT INFORMATION LTD
TI Novel unit dose comprising fibroblast growth factor, its angiogenically active fragment or mutein for inducing cardiac angiogenesis, treating **coronary artery disease** and reducing post myocardial infarction injury -
AB This invention describes a novel unit dose (I), of fibroblast growth factor (FGF) comprising 0.008-6.1 mg of a mammalian FGF comprising sequence of 140 ((II) and (III)), 146 ((IV) and (V)), 205 (VI), 266 (VII), 207 ((VIII) and (XI)), 215 (IX), and 208 (X) amino acids (aa), given in the specification, its angiogenically active fragment or mutein.

The product of the invention has angiogenic and cardiant activity. (I) is used for treating a human patient for **coronary artery disease**, and inducing angiogenesis in the human heart. (I) further provides an adjunct for reducing post myocardial infarction injury in humans. The unit dose provides the human patient with a rapid and therapeutic cardiac angiogenesis sufficient to obviate surgical intervention and results in an superior increase in the treated patients's exercise tolerance time (ETT). It also provides a safe and therapeutically efficacious treatment for the patients with **coronary artery disease** that lasts at least 6 months before a further treatment is needed. The method provides superior increase of 1.5-2 minutes in the treated patient's (ETT), compared to an increase of 30 seconds for current modes treatment. This sequence represents a **FGF-2** protein fragment described in the method of the invention.

ACCESSION NUMBER: AAY87849 protein DGENE
TITLE: Novel unit dose comprising fibroblast growth factor, its angiogenically active fragment or mutein for inducing cardiac angiogenesis, treating **coronary artery disease** and reducing post myocardial infarction injury -
INVENTOR: Kavanaugh W M
PATENT ASSIGNEE: (CHIR) CHIRON CORP.
(WHIT-I) WHITEHOUSE M J.
PATENT INFO: WO 2000021548 A2 20000420 67p
APPLICATION INFO: WO 1999-US22936 19991013
PRIORITY INFO: US 1998-104103 19981013
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-317840 [27]

L3 ANSWER 13 OF 19 DGENE COPYRIGHT 2001 DERWENT INFORMATION LTD
TI Novel unit dose comprising fibroblast growth factor, its angiogenically active fragment or mutein for inducing cardiac angiogenesis, treating **coronary artery disease** and reducing post myocardial infarction injury -
AB This invention describes a novel unit dose (I), of fibroblast growth factor (FGF) comprising 0.008-6.1 mg of a mammalian FGF comprising sequence of 140 ((II) and (III)), 146 ((IV) and (V)), 205 (VI), 266 (VII), 207 ((VIII) and (XI)), 215 (IX), and 208 (X) amino acids (aa), given in the specification, its angiogenically active fragment or mutein.

The product of the invention has angiogenic and cardiant activity. (I) is used for treating a human patient for **coronary artery disease**, and inducing angiogenesis in the human heart. (I) further provides an adjunct for reducing post myocardial infarction injury in humans. The unit dose provides the human patient with a rapid

and therapeutic cardiac angiogenesis sufficient to obviate surgical intervention and results in an superior increase in the treated patients's exercise tolerance time (ETT). It also provides a safe and therapeutically efficacious treatment for the patients with **coronary artery disease** that lasts at least 6 months before a further treatment is needed. The method provides superior increase of 1.5-2 minutes in the treated patient's (ETT), compared to an increase of 30 seconds for current modes treatment. This sequence represents the bovine **FGF-2** protein fragment described in the method of the invention.

ACCESSION NUMBER: AAY87848 protein DGENE
TITLE: Novel unit dose comprising fibroblast growth factor, its angiogenically active fragment or mutein for inducing cardiac angiogenesis, treating **coronary artery disease** and reducing post myocardial infarction injury -
INVENTOR: Kavanaugh W M
PATENT ASSIGNEE: (CHIR) CHIRON CORP.
(WHIT-I) WHITEHOUSE M J.
PATENT INFO: WO 2000021548 A2 20000420 67p
APPLICATION INFO: WO 1999-US22936 19991013
PRIORITY INFO: US 1998-104103 19981013
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-317840 [27]

L3 ANSWER 14 OF 19 DGENE COPYRIGHT 2001 DERWENT INFORMATION LTD
TI Novel unit dose comprising fibroblast growth factor, its angiogenically active fragment or mutein for inducing cardiac angiogenesis, treating **coronary artery disease** and reducing post myocardial infarction injury -
AB This invention describes a novel unit dose (I), of fibroblast growth factor (FGF) comprising 0.008-6.1 mg of a mammalian FGF comprising sequence of 140 ((II) and (III)), 146 ((IV) and (V)), 205 (VI), 266 (VII), 207 ((VIII) and (XI)), 215 (IX), and 208 (X) amino acids (aa), given in the specification, its angiogenically active fragment or mutein.

The product of the invention has angiogenic and cardiant activity. (I) is used for treating a human patient for **coronary artery disease**, and inducing angiogenesis in the human heart. (I) further provides an adjunct for reducing post myocardial infarction injury in humans. The unit dose provides the human patient with a rapid and therapeutic cardiac angiogenesis sufficient to obviate surgical intervention and results in an superior increase in the treated patients's exercise tolerance time (ETT). It also provides a safe and therapeutically efficacious treatment for the patients with **coronary artery disease** that lasts at least 6 months before a further treatment is needed. The method provides superior increase of 1.5-2 minutes in the treated patient's (ETT), compared to an increase of 30 seconds for current modes treatment. This sequence represents the human **FGF-2** protein fragment described in the method of the invention.

ACCESSION NUMBER: AAY87847 protein DGENE
TITLE: Novel unit dose comprising fibroblast growth factor, its angiogenically active fragment or mutein for inducing cardiac angiogenesis, treating **coronary artery disease** and reducing post myocardial infarction injury -
INVENTOR: Kavanaugh W M

PATENT ASSIGNEE: (CHIR)CHIRON CORP.
(WHIT-I) WHITEHOUSE M J.
PATENT INFO: WO 20[redacted]21548 A2 20000420 [redacted]67p
APPLICATION INFO: WO 1999-US22936 19991013
PRIORITY INFO: US 1998-104103 19981013
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-317840 [27]

L3 ANSWER 15 OF 19 DGENE COPYRIGHT 2001 DERWENT INFORMATION LTD
TI Composition for inducing angiogenesis or treating **coronary artery disease** comprises fibroblast growth factor-2 or angiogenically active fragment or mutein -
AB This sequence represents a recombinant bovine fibroblast growth factor-2 (**FGF-2**) coding sequence. The invention relates to a unit dose composition (I) for inducing angiogenesis in a human, comprising 0.008-7.2 mg of **FGF-2** or an angiogenically active fragment or mutein of **FGF-2**. The composition (I) and recombinant **FGF-2** are useful for treating **coronary artery disease** or inducing angiogenesis in a human patient. Recombinant **FGF-2** may be used to treat unstable angina and acute myocardial infarction.
ACCESSION NUMBER: AAA07355 DNA DGENE
TITLE: Composition for inducing angiogenesis or treating **coronary artery disease** comprises fibroblast growth factor-2 or angiogenically active fragment or mutein -
PATENT ASSIGNEE: (CHIR)CHIRON CORP.
(WHIT-I) WHITEHOUSE M J.
PATENT INFO: WO 2000013701 A2 20000316 60p
APPLICATION INFO: WO 1999-US19770 19990827
PRIORITY INFO: US 1998-145743 19980903
US 1998-104102 19981013
US 1998-104103 19981013
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-256860 [22]

L3 ANSWER 16 OF 19 DGENE COPYRIGHT 2001 DERWENT INFORMATION LTD
TI Novel unit dose comprising fibroblast growth factor, its angiogenically active fragment or mutein for inducing cardiac angiogenesis, treating **coronary artery disease** and reducing post myocardial infarction injury -
AB This invention describes a novel unit dose (I), of fibroblast growth factor (FGF) comprising 0.008-6.1 mg of a mammalian FGF comprising sequence of 140 ((II) and (III)), 146 ((IV) and (V)), 205 (VI), 266 (VII), 207 ((VIII) and (XI)), 215 (IX), and 208 (X) amino acids (aa), given in the specification, its angiogenically active fragment or mutein.
The product of the invention has angiogenic and cardiant activity. (I) is used for treating a human patient for **coronary artery disease**, and inducing angiogenesis in the human heart. (I) further provides an adjunct for reducing post myocardial infarction injury in humans. The unit dose provides the human patient with a rapid and therapeutic cardiac angiogenesis sufficient to obviate surgical intervention and results in an superior increase in the treated patients's exercise tolerance time (ETT). It also provides a safe and therapeutically efficacious treatment for the patients with **coronary artery disease** that lasts at least 6 months before a further treatment is needed. The method provides superior increase of 1.5-2 minutes in the treated patient's (ETT), compared to an increase of 30 seconds for current modes treatment. This sequence encodes

the bovine **FGF-2** protein fragment described in the method of the invention.

ACCESSION NUMBER: AAA39[redacted] DNA DGENE [redacted]
TITLE: Novel unit dose comprising fibroblast growth factor, its angiogenically active fragment or mutein for inducing cardiac angiogenesis, treating **coronary artery disease** and reducing post myocardial infarction injury -
INVENTOR: Kavanaugh W M
PATENT ASSIGNEE: (CHIR) CHIRON CORP.
(WHIT-I) WHITEHOUSE M J.
PATENT INFO: WO 2000021548 A2 20000420 67p
APPLICATION INFO: WO 1999-US22936 19991013
PRIORITY INFO: US 1998-104103 19981013
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2000-317840 [27]

L3 ANSWER 17 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
TI Pharmacokinetics and pharmacodynamics of recombinant **FGF-2** in a phase I trial in **coronary artery disease**.
AB Fibroblast growth factor-2 (**FGF-2**) is a heparin-binding protein capable of inducing angiogenesis in multiple animal models of chronic ischemia. The pharmacokinetics and pharmacodynamics of a single dose of recombinant **FGF-2** (rFGF-2) administered by intracoronary or intravenous infusion were evaluated in a Phase I trial in 66 patients with severe **coronary artery disease**. rFGF-2 displayed biphasic elimination with a mean studywide distribution t(1/2) of 21 minutes and a mean apparent terminal elimination t(1/2) of 7.6 hours. Systemic exposure to rFGF-2 was comparable following intracoronary or intravenous administration. Peak plasma concentration and area under the concentration-time curve increased proportionally with dose, indicating linear pharmacokinetics over the dose range examined (0.33 to 48.0 .mu.g/kg). Greater systemic exposure was observed when heparin was administered closer to rFGF-2 infusion, consistent with slower clearance of heparin/rFGF-2 complexes. Infusion of rFGF-2 was associated with changes in acute hemodynamics. While a clear PK/PD dose-response relationship was not established, a trend toward hypotension and tachycardia with higher rFGF-2 doses was observed. .COPYRGT.2001 the American College of Clinical Pharmacology.
ACCESSION NUMBER: 2001132634 EMBASE
TITLE: Pharmacokinetics and pharmacodynamics of recombinant **FGF-2** in a phase I trial in **coronary artery disease**.
AUTHOR: Bush M.A.; Samara E.; Whitehouse M.J.; Yoshizawa C.; Novicki D.L.; Pike M.; Laham R.J.; Simons M.; Chronos N.A.
CORPORATE SOURCE: Dr. M.A. Bush, Chiran Corparation, 4560 Harton Street M/S 4.178, Emeryville, CA 94608-2916, United States
SOURCE: Journal of Clinical Pharmacology, (2001) 41/4 (378-385). Refs: 22
ISSN: 0091-2700 CODEN: JCPCBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

L3 ANSWER 18 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

TI Mechanical endothelial damage results in basic fibroblast growth factor-mediated activation of extracellular signal-regulated kinases.

AB Background: Endothelial damage, such as that associated with balloon angioplasty or preparation of veins for bypass grafts, results in intimal hyperplasia. Growth factors and cytokines that modulate endothelial cell functions through various intracellular signaling pathways mediate rapid endothelial repair, which may prevent or reduce restenosis. Here we investigated the effect of mechanical injury of endothelial cells on the mitogen-activated kinase signaling pathways, extracellular-signal-regulated kinases (ERKs), C-Jun N-terminal kinase (JK/SAPK), and p38. Methods: Confluent human umbilical vein endothelial cells or bovine aortic endothelial cells were wounded with a razor blade; mitogen-activated kinase activation was monitored by immunoblotting with antibodies to active ERK, JNK/SAPK, or p38. Results: Wounding of human umbilical vein endothelial cell or bovine aortic endothelial cell monolayers resulted in rapid (5-minute) activation of ERK-1 and -2, which was abolished by monoclonal antibody to basic fibroblast growth factor (**FGF-2**). This antibody or an inhibitor of ERK activation, PD98059, also blocked endothelial cell migration after the wounding. Thus **FGF-2**-induced ERK activation mediates the endothelial response to wounding. Conclusions: ERK-1 and -2 are activated by **FGF-2** released from endothelial cells in response to injury. Therapeutic strategies aimed at reducing **FGF-2**-induced intimal hyperplasia should preserve ERK activation in endothelial cells while abolishing it in smooth muscle cells.

ACCESSION NUMBER: 1999285095 EMBASE
TITLE: Mechanical endothelial damage results in basic fibroblast growth factor- mediated activation of extracellular signal-regulated kinases.
AUTHOR: Pintucci G.; Steinberg B.M.; Seghezzi G.; Yun J.; Apazidis A.; Baumann F.G.; Grossi E.A.; Colvin S.B.; Mignatti P.; Galloway A.C.
CORPORATE SOURCE: Dr. B.M. Steinberg, NYU Medical Center, 530 First Ave, New York, NY 10016, United States
SOURCE: Surgery, (1999) 126/2 (422-427).
Refs: 21
ISSN: 0039-6060 CODEN: SURGAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

L3 ANSWER 19 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

TI Fibroblast growth factor-mediated angiogenesis for the treatment of ischemia. Lessons learned from experimental models and early human experience.

AB Fibroblast growth factors (FGFs) are a family of nearly twenty heparin-binding growth factors. They are widely distributed throughout the body, but their activity is tightly controlled. This review will focus on fibroblast growth factor-1 /FGF-1) and fibroblast growth factor-2 ( **FGF-2**) which have been studied extensively in vitro and in vivo. These two growth factors stimulate the proliferation of cells of mesenchymal origin, including the three principal vascular cell types: fibroblasts, endothelial cells and smooth muscle cells. The molecular characteristics of these growth factors, their receptors, distribution, function, pharmacokinetics, hemodynamic effects and toxicity are reviewed herein. The experimental evidence for the potential for FGFs as therapeutic agents for the treatment of progressive myocardial ischemia, acute myocardial ischemia, and peripheral limb ischemia is also analyzed. It is not known to what extent the results of animal studies can be extrapolated to humans with ischemic cardiovascular disease. Clinical

trials have been initiated, and there is a growing hope that the pharmacologic use of growth factors will represent a viable therapeutic alternative for patients with ischemic cardiovascular disease.

ACCESSION NUMBER: 1998372756 EMBASE
TITLE: Fibroblast growth factor-mediated angiogenesis for the treatment of ischemia. Lessons learned from experimental models and early human experience.
AUTHOR: Goncalves L.M.
CORPORATE SOURCE: L.M. Goncalves, Cardiology Branch, National Heart, Lung/Blood Institute, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892-1518, United States. goncalvl@gwgate.nhlbi.nih.gov
SOURCE: Revista Portuguesa de Cardiologia, (1998) 17/SUPPL. 2 (11-20).
Refs: 103
ISSN: 0304-4750 CODEN: RPCADZ
COUNTRY: Portugal
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English; Portuguese

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 63.78 | 64.08 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| CA SUBSCRIBER PRICE | -2.94 | -2.94 |

FILE 'BIOSIS' ENTERED AT 10:42:30 ON 06 SEP 2001
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FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 5 September 2001 (20010905/ED)

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        163226 CORONARY
        182233 ARTERY
       1671380 DISEASE
L4       35396 CORONARY ARTERY DISEASE
                (CORONARY(W)ARTERY(W)DISEASE)
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(FILE 'HOME' ENTERED AT 10:38:12 ON 06 SEP 2001)

FILE 'MEDLINE, USPATFULL, HCAPLUS, WPIDS, DGENE, EMBASE, FROSTI, FSTA' ENTERED AT 10:39:15 ON 06 SEP 2001
L1 75286 S CORONARY ARTERY DISEASE

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L2            1 S CORONARY ARTERY DISEASE () TREATMENT () METHOD
L3           19 S L1 AND FGF-2

     FILE 'BIOSIS' ENTERED AT 10:42:30 ON 06 SEP 2001
L4        35396 S L1

=> s l3

         163226 CORONARY
         182233 ARTERY
        1671380 DISEASE
          35396 CORONARY ARTERY DISEASE
                  (CORONARY(W)ARTERY(W)DISEASE)
           5954 FGF
        2605955 2
           1354 FGF-2
                  (FGF(W)2)
L5            1 L1 AND FGF-2

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L5   ANSWER 1 OF 1  BIOSIS  COPYRIGHT 2001 BIOSIS
TI   Pharmacokinetics and pharmacodynamics of recombinant FGF-
     2 in a phase I trial in coronary artery
     disease.
AB   Fibroblast growth factor-2 (FGF-2) is a
     heparin-binding protein capable of inducing angiogenesis in multiple
     animal models of chronic ischemia. The pharmacokinetics and
     pharmacodynamics of a single dose of recombinant FGF-2
     (rFGF-2) administered by intracoronary or intravenous infusion were
     evaluated in a Phase I trial in 66 patients with severe coronary
     artery disease. rFGF-2 displayed biphasic elimination
     with a mean studywide distribution t1/2 of 21 minutes and a mean apparent
     terminal elimination t1/2 of 7.6 hours. Systemic exposure to rFGF-2 was
     comparable following intracoronary or intravenous administration. Peak
     plasma concentration and area under the concentration-time curve
increased
     proportionally with dose, indicating linear pharmacokinetics over the
dose
     range examined (0.33 to 48.0 mug/kg). Greater systemic exposure was
     observed when heparin was administered closer to rFGF-2 infusion,
     consistent with slower clearance of heparin/rFGF-2 complexes. Infusion of
     rFGF-2 was associated with changes in acute hemodynamics. While a clear
     PK/PD dose-response relationship was not established, a trend toward
     hypotension and tachycardia with higher rFGF-2 doses was observed.
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